

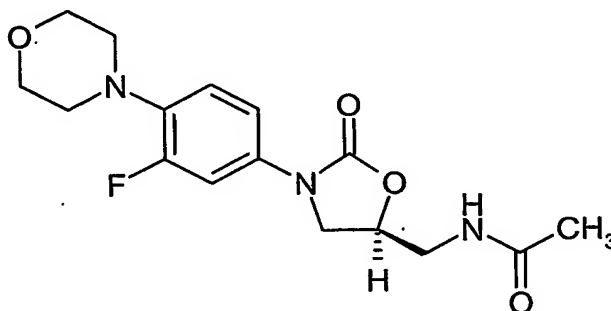
**A NOVEL PROCESS FOR THE PREPARATION OF LINEZOLID AND
RELATED COMPOUNDS**

FIELD OF THE INVENTION

5 The present invention provides a novel process for preparation of 5-aminomethyl substituted oxazolidinones, key intermediates for oxazolidinone antibacterials.

BACKGROUND OF THE INVENTION

10 US Pat. No. 5,688,792 (US 5,688,792) disclosed oxazine and thiazine oxazolidinone derivatives. The compounds are antimicrobial agents. Among them linezolid, chemically N-[[[(5S)-3-[3-fluoro-4-(4-morpholinyl)phenyl]-2-oxo-5-oxazolidinyl]methyl]acetamide is the most important antibacterial agent. Linezolid is represented by the following structure:



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Processes for preparation of linezolid were described in US 5,837,870, WO 99/24393, WO 95/07271, J.Med.Chem. 39(3), 673-679, 1996 and Tetrahedron Lett., 40(26), 4855, 1999.

20 According to prior art processes, the 5-hydroxymethyl substituted oxazolidinones are converted to the corresponding 5-aminomethyl substituted oxazolidinones, key intermediates in the production of oxazolidinone antibacterial pharmaceuticals.

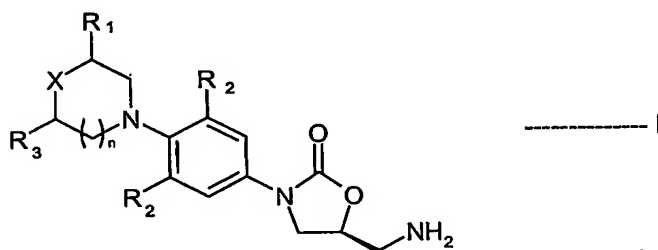
25 The prior art processes for preparing 5-aminomethyl substituted oxazolidinones are associated with many drawbacks. For instant in the preparation of linezolid, WO 95/07271 uses butyl lithium at very low temperature (-78°C) and WO 99/24393 uses phosgene gas. It is known that the handling of

butyl lithium and phosgene gas are difficult and the person skilled in the art appreciate a process that produces the product in good yield avoiding the 'difficult to handle' reagents.

We have discovered a novel process for preparation of 5-aminomethyl substituted oxazolidinone key intermediates using novel intermediates. The novel process solve the drawbacks associated with the prior processes and so, commercially viable for preparing these and related compounds.

SUMMARY OF INVENTION

The present invention provides a novel process to prepare 5-aminomethyl substituted oxazolidinones of formula I:



wherein

X is O, S, SO or SO₂;

R₁ is H, CH₃ or CN;

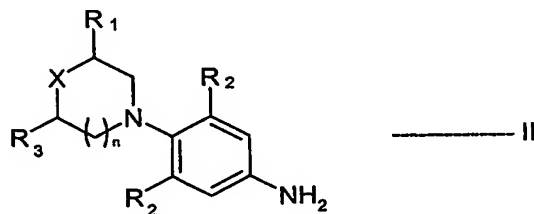
R₂ is independently H, F or Cl;

R₃ is H or CH₃;

n is 0, 1 or 2;

which comprises;

a) reacting a compound of formula II:



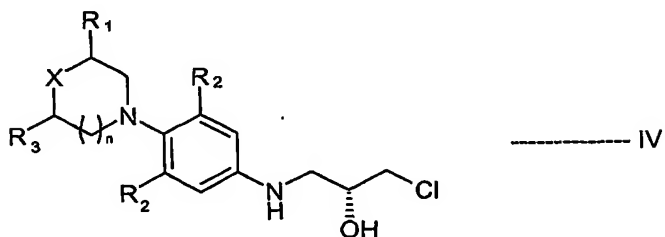
wherein R₁, R₃, X, R₂ and n are as defined in formula I;

with R-epichlorohydrin of formula III:



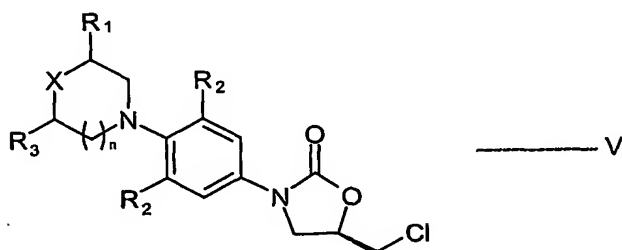
to produce a compound of formula IV:

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wherein R₁, R₃, X, R₂ and n are as defined in formula I;

- b) converting the product of step (a) to chloromethyl oxazolidinone compound of formula V:
- 10



wherein R₁, R₃, X, R₂ and n are as defined in formula I;

and

- c) converting the chloromethyl oxazolidinone compound of step (b) to aminomethyl oxazolidinone of formula I.
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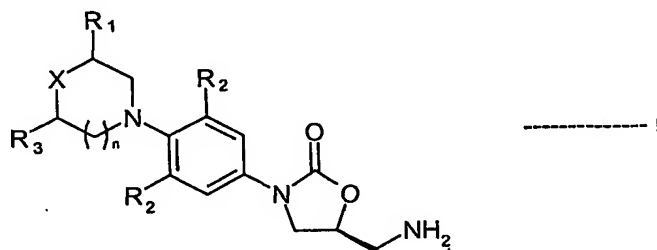
The compounds of formula IV are novel and provides another aspect of the present invention.

The compounds of the formula V with the exception of the compound of formula V wherein $R_1 = R_3$ is H; one R_2 is H and the other R_2 is F; X is O; and n is 1 are novel.

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DETAILED DESCRIPTION OF THE INVENTION

The present invention provides a novel process for preparing 5-aminomethyl substituted oxazolidinones of formula I:



10 wherein

X is O, S, SO or SO₂;

R_1 is H, CH₃ or CN;

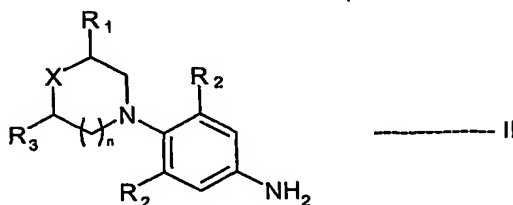
R_2 is independently H, F or Cl;

R_3 is H or CH₃;

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n is 0, 1 or 2.

Step - a) Phenyl amine compound of formula II:



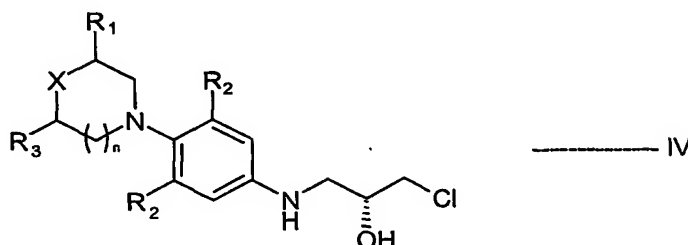
wherein R_1 , R_3 , X, R_2 and n are as defined in formula I;

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is reacted with R-epichlorohydrin of formula III:



to provide chlorohydrin compound of formula IV:



wherein R_1 , R_3 , X , R_2 and n are as defined in formula I.

5 The quantity of epichlorohydrin is not critical, but for better yield at least one molar equivalent is required per equivalent of phenyl amine of formula II.

The reaction may be carried out with or without using a solvent.

If the reaction is carried out in the absence of solvent, the compounds of formula II and the formula III are usually heated together for sufficient time to
 10 obtain the compound of formula IV. The reactants are heated preferably to about 40 - 150°C and more preferably to about 40 - 120°C. The time required for the conversion is 30 minutes to 10 hours, preferably 2 to 6 hours.

Preferably, the reaction between the compounds of formula II and formula III is carried out in a solvent. Any solvent, which is neutral towards the
 15 reactants, may be used. Operable solvents include cyclic ethers such as tetrahydrofuran; amides such as N, N-dimethylformamide and N, N-dimethylacetamide; acetonitrile; and alcohols such as methanol, ethanol, t-amyl alcohol, t-butyl alcohol and Isopropyl alcohol; and a mixture thereof. Preferable solvent is selected from methanol, isopropyl alcohol and N, N-
 20 dimethylformamide.

The reaction is performed at or below boiling temperature of the solvent used, more preferably between 10°C and boiling temperature of the solvent used and even more preferably at boiling temperature of the solvent used.

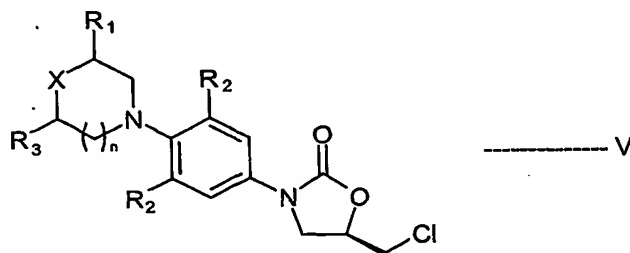
Time required for completion of the reaction depends on factors such as
 25 solvent used and temperature at which the reaction is carried.

The product obtained may be used directly in the next step, or it can be isolated from the reaction mixture and used in the next step.

The compounds of formula IV are novel and provides another aspect of the present invention.

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Step - b) The chlorohydrin compound of formula IV produced as above is subjected to carbonylation to provide chloromethyl oxazolidinone compound of formula V:



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wherein R_1 , R_3 , X , R_2 and n are as defined in formula I.

The carbonylation is performed using any carbonylating reagent commonly known for such purpose. Among them carbonyldiimidazole, phosgene, methyl chloroformate, benzyl chloroformate and phenylchloroformate are preferred; carbonyldiimidazole being more preferred.

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The carbonylation reaction is preferably performed by contacting the chlorohydrin compound of formula IV with carbonylating agent in the presence of an aprotic solvent or a mixture thereof. More preferably the chlorohydrin compound of formula IV is reacted with at least one molar equivalent of the carbonylating agent in the presence of an aprotic solvent such as methylene dichloride, ethylenedichloride or chloroform.

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The compound of formula V wherein $R_1 = R_3$ is H; X is O; one R_2 is H and the other R_2 is F; n is 1 ((5R)-5-(chloromethyl)-3-[3-fluoro-4-(4-morpholinyl)phenyl]-2-oxazolidinone) is mentioned in the J. Pharmaceutical and biomedical analysis, 2002, 30 (3), 635-642 as an possible impurity in linezolid. We disclosed the use of this compound and related compounds in the preparation of the compounds of formula I.

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The compounds of formula V, wherein X, R₁, R₂, R₃ and n are as defined in formula I with the exception of the compound of formula V, wherein R₁ = R₃ is H; one R₂ is H and the other R₂ is F; X is O; and n is 1 are novel and provide another aspect of present invention.

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Step - c) The chloromethyl oxazolidinone compound of formula V produced as above is converted to aminomethyl oxazolidinone compound of formula I.

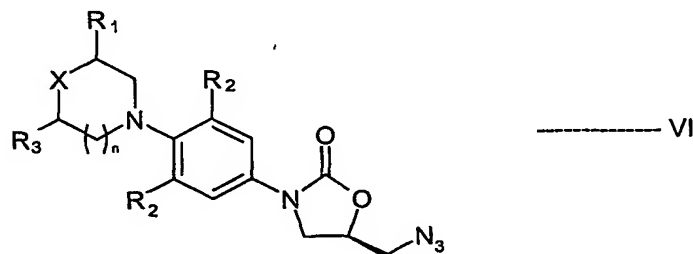
Preferred 5-amino methyl substituted oxazolidinones are the compounds of formula I, wherein R₁ = R₃ is H; R₂ is independently H and F; X is O or S; and n is 1. More preferred 5-amino methyl substituted oxazolidinones are the compounds of formula I, wherein R₁ = R₃ is H; R₂ is independently H and F; X is O; and n is 1. Still more preferred 5-amino methyl substituted oxazolidinones are the compounds of formula I, wherein R₁ = R₃ is H; one R₂ is H and the other R₂ is F; X is O; and n is 1.

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The conversion of the compound of formula V to the compound of formula I can be achieved by a method known for the conversion of aliphatic chloride to the corresponding amine.

Thus, for example, chlorine atom of the chloromethyl oxazolidinone compound is first replaced by azide using azide source such as sodium azide or potassium azide to provide azide compound of formula VI:

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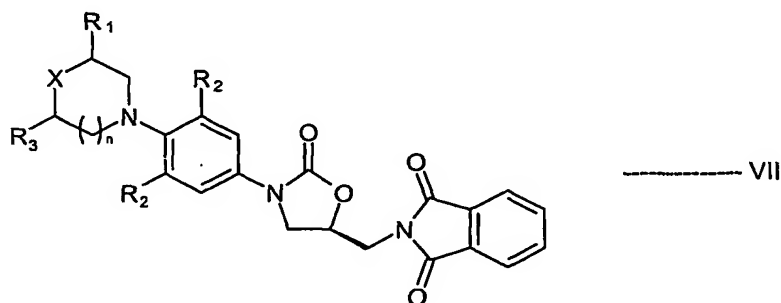
wherein R₁, R₃, X, R₂ and n are as defined in formula I.

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The azide compound is known and can be converted to the aminomethyl oxazolidinone compound by known methods such as those described in US 5,688,792. For example, the azide compound is hydrogenated using for

example palladium/carbon catalyst to provide the aminomethyl oxazolidinone compound.

Alternatively, the chloromethyl oxazolidinone compound is reacted with potassium phthalimide to provide phthalimido compound of formula VII:



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wherein R_1 , R_3 , X , R_2 and n are as defined in formula I.

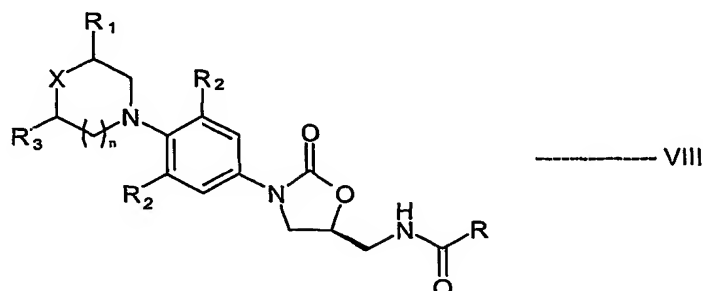
The reaction is carried out by contacting the 5-chloromethyl oxazolidinones with potassium phthalimide in a solvent or mixture of solvents. Selection of solvent is not critical, but preferable solvents are those that dissolve both the chloromethyl oxazolidinones and potassium phthalimide to ensure maximum contact between the reactants resulting in faster reaction. However, the process is also operable with solvents that only partially dissolve the chloromethyl oxazolidinones or potassium phthalimide. The preferable solvent is dimethyl formamide or acetonitrile.

The reaction is performed preferably between about 10°C and the boiling temperature of the solvent used, more preferably between 40°C and 100°C and most preferably at the boiling temperature of the solvent used.

Time required for completion of the reaction depends on factors such as solvent used and temperature at which the reaction is carried out. For example, if the reaction is carried out by contacting the 5-chloromethyl oxazolidinones with potassium phthalimide in dimethylformamide under reflux conditions, about 2 to 10 hours is required for the reaction completion.

The phthalimido compounds of formula are known and can be converted to the aminomethyl oxazolidinone compounds by using for example Hydrazine hydrate or aqueous methylamine. These methods are known and are described for example in US 5,688,792.

The aminomethyl oxazolidinone compounds of formula I are acylated by known methods using acylating agents such as acyl halides or acyl anhydrides to form the corresponding 5-acylaminomethyloxazolidinone compounds of formula VIII.



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wherein R_1 , R_3 , X , R_2 and n are as defined in formula I; R represents C_1 to C_8 straight or branched alkyl groups. The preferred alkyl group is CH_3 .

The acylation can be carried out by known methods such as those described in US 5,688,792.

10 One compound of formula VIII can be converted to another compound of formula VIII. Thus for example compounds of formula VIII, wherein X is S can be converted to the compounds of formula VIII, wherein X is SO or SO_2 by the methods such as those disclosed in US 5,688, 792.

15 The 5-acyl amino methyl substituted oxazolidinone of formula VIII are known to be antibacterial pharmaceutical agents.

R-Epichlorohydrin has the right configuration to obtain the compounds of formula I and VIII. The configuration of epichlorohydrine is retained through out the sequence of reactions of the invention. However, it is readily apparent to one skilled in the art that one could easily perform the identical process steps with
20 the opposite enantiomeric form or racemic form to obtain the corresponding stereo isomers.

Therefore, using the chemistry of the claimed process with any of the enantiomeric forms is considered equivalent to the claimed processes.

25 In particular most important compound of formula VIII is linezolid (VIII, R_1 and R_3 is H ; X is O , one R_2 is H and the other R_2 is F ; n is 1).

The most preferred process for preparing linezolid is described as under:

- a) 3-fluoro-4-morpholinyl aniline (formula II, $R_1 = R_3$ is H; X is O; one R_2 is H and the other R_2 is F; and n is 1) is reacted with R-epichlorohydrin (formula III) to produce N-[3-Chloro-2-(R)-hydroxypropyl]-3-fluoro-4-morpholinyl aniline (formula IV, $R_1 = R_3$ is H; X is O; one R_2 is H and the other R_2 is F; and n is 1);

The quantity of epichlorohydrin is not critical, but for better yield at least one molar equivalent is required per equivalent of 3-fluoro-4-morpholinyl aniline.

Any solvent, which is neutral towards the reactants, may be used. Operable solvents include cyclic ethers such as tetrahydrofuran; amides such as N, N-dimethylformamide and N, N-dimethylacetamide; acetonitrile; and alcohols such as methanol, ethanol, t-amyl alcohol, t-butyl alcohol and isopropyl alcohol. Preferable solvent is selected from methanol, isopropyl alcohol and N, N-dimethylformamide.

The reaction is performed at or below boiling temperature of the solvent used, more preferably between 10°C and boiling temperature of the solvent used and even more preferably at boiling temperature of the solvent used.

Time required for completion of the reaction depends on factors such as solvent used and temperature at which the reaction is carried. For example, if the reaction is carried out in isopropyl alcohol solvent at the boiling temperature of the solvent, about 15 hours is required for the reaction completion.

The product obtained can be used directly in the next step, or it can be isolated from the reaction mixture and used in the next step.

- b) N-[3-Chloro-2-(R)-hydroxypropyl]-3-fluoro-4-morpholinyl aniline produced as above is subjected to carbonylation to provide (5R)-5-(chloromethyl)-3-[3-fluoro-4-(4-morpholinyl)phenyl]-2-oxazolidinone (Formula V, $R_1 = R_3$ is H; X is O; one R_2 is H and the other R_2 is F; and n is 1).

The carbonylation is performed using any carbonylating reagent commonly known for such purpose. Among them carbonyldiimidazole, phosgene, methyl chloroformate, benzyl chloroformate and phenylchloroformate are preferred; carbonyldiimidazole being more preferred.

The carbonylation reaction is preferably performed by contacting the N-[3-Chloro-2-(R)-hydroxypropyl]-3-fluoro-4-morpholinyl aniline with carbonylating agent in the presence of an aprotic solvent or a mixture of aprotic solvents. More preferably the N-[3-Chloro-2-(R)-hydroxypropyl]-3-fluoro-4-morpholinyl aniline is

reacted with at least one molar equivalent of the carbonylating agent in the presence of an aprotic solvent such as methylene dichloride, ethylenedichloride or chloroform.

c) (5R)-5-(chloromethyl)-3-[3-fluoro-4-(4-morpholinyl)phenyl]-2-oxazolidinone

5 produced as above is reacted with potassium phthalimide to provide (S)-N-[[3-[3-Fluoro-4-[4-morpholinyl]phenyl]-2-oxo-5-oxazolidinyl]methyl]phthalimide (Formula VII, $R_1 = R_3$ is H; X is O; one R_2 is H and the other R_2 is F; and n is 1);

The reaction is carried out by contacting the (5R)-5-(chloromethyl)-3-[3-fluoro-4-(4-morpholinyl)phenyl]-2-oxazolidinone with potassium phthalimide in a solvent or a mixture of solvents. Selection of solvent is not critical, but preferable solvents are those that dissolve both the chloromethyl oxazolidinones and potassium phthalimide to ensure maximum contact between the reactants resulting in faster reaction. However, the process is also operable with solvents that only partially dissolve the chloromethyl oxazolidinones or potassium phthalimide. The preferable solvent is dimethyl formamide or acetonitrile.

The reaction is performed preferably between about 10°C and the boiling temperature of the solvent used, more preferably between 40°C and 100°C and most preferably at the boiling temperature of the solvent used.

20 Time required for completion of the reaction depends on factors such as solvent used and temperature at which the reaction is carried out. For example, if the reaction is carried out by contacting the 5-chloromethyl oxazolidinones with potassium phthalimide in dimethylformamide under reflux conditions, about 3 to 7 hours is required for the reaction completion.

25 d) (S)-N-[[3-[3-Fluoro-4-[4-morpholinyl]phenyl]-2-oxo-5-oxazolidinyl]methyl]

phthalimide produced as above is reacted with hydrazine hydrate or aqueous methyl amine to produce S-N-[[3-[3-Fluoro-4-[4-morpholinyl]phenyl]-2-oxo-5-oxazolidinyl]methyl]amine (Formula I, $R_1 = R_3$ is H; X is O; one R_2 is H and the other R_2 is F; and n is 1). These methods of deprotection are known and described for example in US 5,688,792.

30 e) S-N-[[3-[3-Fluoro-4-[4-morpholinyl]phenyl]-2-oxo-5-oxazolidinyl]methyl]amine is reacted with acetic anhydride to produce linezolid.

The following examples are given for the purpose of illustrating the present invention and should not be considered as limitations on the scope and spirit of the invention.

5

EXAMPLES

Example 1

3-Fluoro-4-morpholinyl aniline (39 g) is mixed with R-epichlorohydrin (18.5 g), isopropyl alcohol (200 ml) is added and heated for 16 hours at reflux temperature. The solvent is distilled to give 57 gm of N-[3-Chloro-2-(R)-hydroxypropyl]-3-fluoro-4-morpholinyl aniline.

10

Example 2

N-[3-Chloro-2-(R)-hydroxypropyl]-3-fluoro-4-morpholinyl aniline (57 g) is dissolved in methylene dichloride (600 ml), diimidazolyl carbonyl (32 g) is added at ambient temperature and the reaction mixture is stirred for 20 hours. Then washed with water and distilled methylene dichloride to give 48 gm of (5R)-5-(chloromethyl)-3-[3-fluoro-4-(4-morpholinyl)phenyl]-2-oxazolidinone.

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Example 3

The mixture of (5R)-5-(chloromethyl)-3-[3-fluoro-4-(4-morpholinyl)phenyl]-2-oxazolidinone (60 g), potassium phthalimide (40 g) and Dimethyl formamide (400 ml) is heated for 5 hours at reflux temperature. The reaction mixture is cooled to ambient temperature, poured in to 2 L water and filtered the solid to give 50 gm (S)-N-[[3-[3-Fluoro-4-[4-morpholinyl]phenyl]-2-oxo-5-oxazolidinyl]methyl]phthalimide.

20

Example 4

Methanol (240 ml) and Hydrazine hydrate (26 g) are added to a flask containing the (S)-N-[[3-[3-Fluoro-4-[4-morpholinyl]phenyl]-2-oxo-5-oxazolidinyl]methyl]phthalimide (40 g), heated for 1 hour at reflux temperature and cooled to room temperature. Then water (500 ml) is added to the reaction mass and extracted with methylene dichloride (300 ml). The combined extractions were washed with water (100 ml) and the solvent distilled to give 20 gm of S-N-[[3-[3-Fluoro-4-[4-morpholinyl]phenyl]-2-oxo-5-oxazolidinyl]methyl] amine.

30

Example 5

S-N-[[3-[3-Fluoro-4-[4-morpholinyl]phenyl]-2-oxo-5-oxazolidinyl]methyl] amine (20 gm) is dissolved in Ethyl acetate (200 ml), Acetic anhydride (20 gm) is

added drop wise at ambient temperature and stirred for 1 hour. The reaction mixture is then cooled to 0-5°C, filtered the solid and re-crystallized from Isopropyl alcohol (400 ml) to give 16 gm of N-[[[(5S)-3-[3-fluoro-4-(4-morpholinyl)phenyl]-2-oxo-5-oxazolidinyl]methyl]acetamide.

5